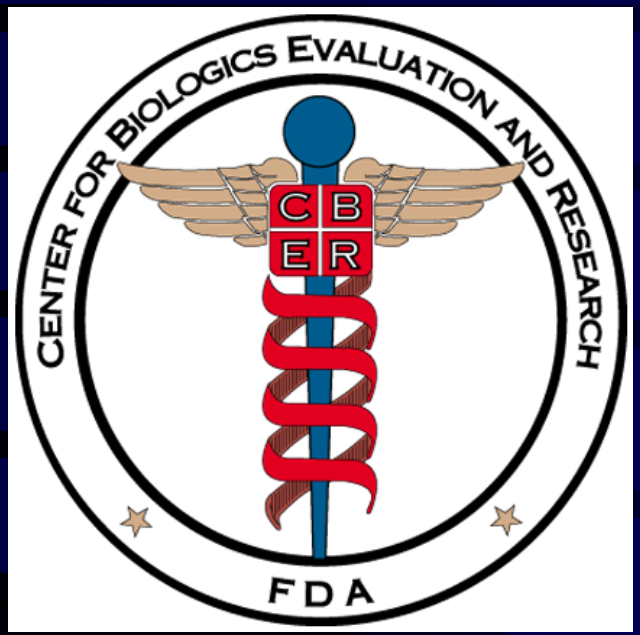
Risk Based Quality for Emerging Biotech Processes and Products



9th Annual GMP By The Sea: Keeping the "C" in GMP

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Presentation Outline - 1

- Opening comments: *What are we all talking about?*
- Relationship of Validation and Risk Management – *How do they fit together*?
- Brief list of means to formalize risk assessment activities

Presentation Outline - 2

- Survey of some focus areas related to risk management and risk mitigation for products:
  - Raw Materials / Component Risks
  - Process and Equipment Risks
  - Bioburden Control and Manufacturing Environment
  - Testing and Validation/Qualification Programs
  - Risk areas not necessarily identified via process mapping (e.g., quality oversight, legacy systems, contract partners, etc.)

What are we all talking about: "*Risk Based Quality*" - 1

- What is "Risk"?
  - Combination of occurrence of *harm* and *severity*
- ICH Q7A addresses risk primarily in terms of *"risk of contamination or cross-contamination…"*

What are we all talking about: "*Risk Based Quality*" - 2

- What does Quality mean?
  - "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." From the glossary of ICH Q6A
  - "Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance." 21 CFR 820.3(s) *for medical devices*

What are we all talking about: "*Risk Based Quality*" - 3

- Risk Management = dynamic and interactive use of Risk Assessment and Risk Mitigation
- Prospective *versus* Reactive Risk Assessment
  - Initial Process Mapping to outline initial validation plan and/or process control strategy
  - Problem identification process may be used by industry or regulators (e.g., deviation system or quality system inspections)
- *Relationship to Critical Process Parameters ?*

Relationship between validation and risk: What is Validation? - 1

- Validation is a requirement under cGMPs for finished pharmaceuticals, and considered requirements under Section 501(a)(2)(B) of FD&C for APIs (quote from Compliance Policy Guide 7132c.08)

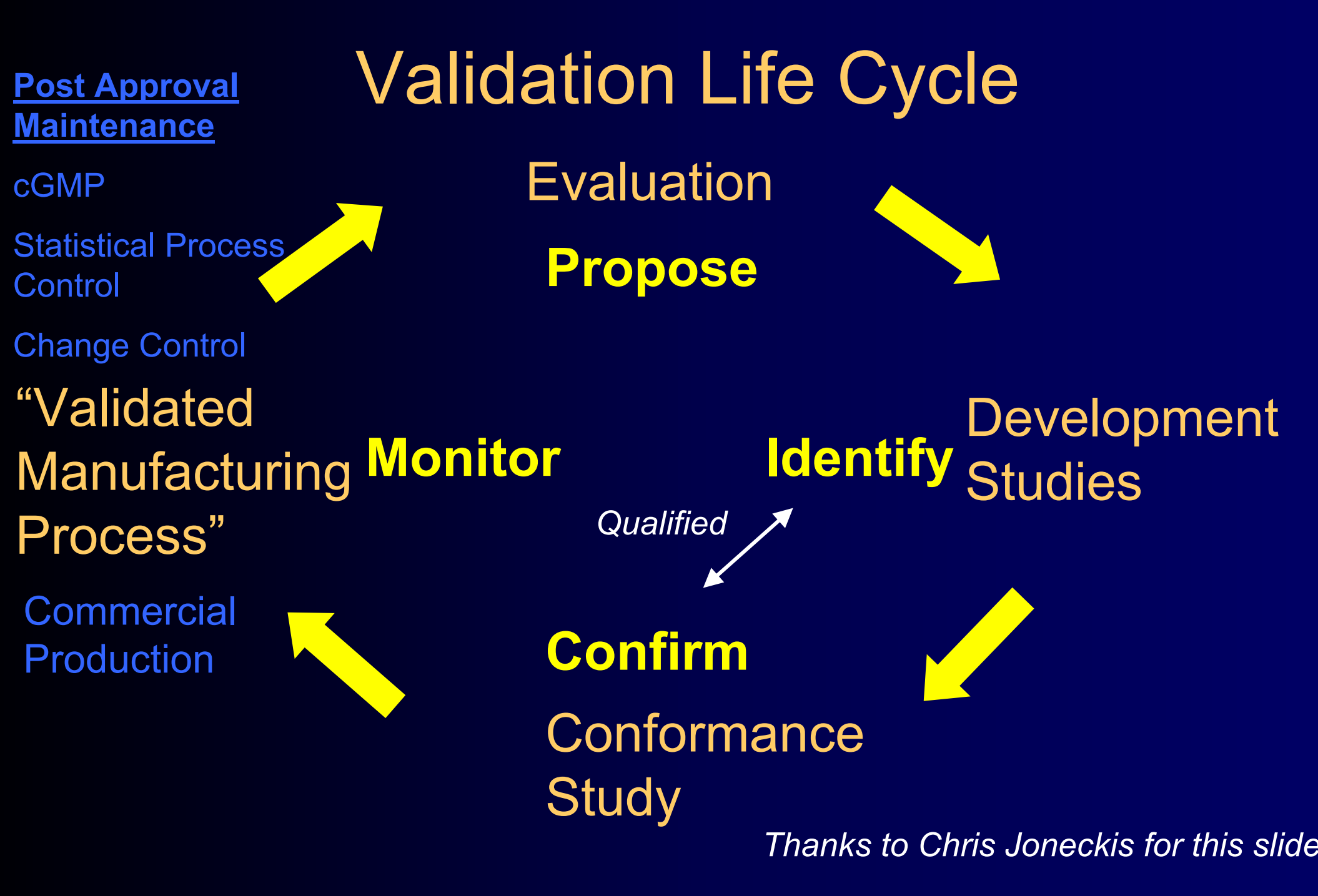
Relationship between validation and risk: What is Validation? - 2

- "Process Validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications." Quote from 21 CFR 820.3(1) *for medical devices*
- Validation involves data collection

Relationship between validation and risk: What is Validation? - 3

- "Proof of validation is obtained through rational experimental design and evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase." (Compliance Policy Guide 7132c.08)
- How does one achieve "rational experimental design" ?
- Let's visit one model for validation life cycle to see if we can figure out what role risk management plays…..

Validation Life Cycle



Thanks to Chris Joneckis for this slide

Process Mapping

Risk Assessment

Possible Control Parameters

Risk Mitigation

Development Studies / Initial Validation Studies

***Initial* Critical Control Parameters**

Conformance Study / Lifecycle Revalidation

Process Control

Risk Management

Risk Based Product Quality!

Post Approval Maintenance

cGMP

Statistical Process Control / Production Experience

Change Control

Is there really something new here?

- Yes and No
- ***Informal*** risk assessments have been performed for decades
- A more formalized risk assessment *may* assist in identifying possible hazards prior to initiation of developmental studies and/or validation/qualification studies

Summary of Risk Assessment Approaches

- Process Mapping is pre-requisite of risk assessment
- Various formalized approaches exist (e.g., PHA, HACCP, HAZOP, FTA, FMEA, FMECA, etc.) – Risk Management tools
- Risk Ranking and Filtering – compare and prioritize risks
- Supporting Statistical Tools (DOE, Process Capability Analysis, Control Charts, etc.)
- Informal Risk Management – *Why use more formalized approach?*

Some early priorities include:

- Prioritization of safety related qualification and validation activities
- Performing equipment capability assessments for each unit operation as processing parameters are defined
- Often new risk factors may be identified when equipment is undergoing initial usage, especially for emerging technologies where equipment performance and fitness-for-use criteria may not be well understood

Immediate Risk Related Concerns: Hazard Analysis and Evaluation

- Safety related issues:
  - Adventitious agents,
  - Maintaining sterility or bioburden control,
  - Immunogenicity concerns, etc.
- Process consistency:
  - Process alteration and optimization
  - Process scale up impacts
    - May be confounded by ongoing qualification and validation activities


A QUALITY PRODUCT
QA/QC
Validation / Qualification
Routine Monitoring
Risk Assessment
Equipment
Environment
Process
Raw Materials
Components

Potential risk mitigation for raw materials and components

Raw Material Testing: Factors that play a role in the extent of raw material testing includes:

- Variability and complexity of material
- Impact of variation on final product
- Ability to test for critical attributes (i.e., demonstration of fitness-for-use with testing results)

Raw Material and Component Testing

Should be based on the critical quality attributes for each raw material or component as determined by process validation studies. These studies should be designed based on issues identified through the risk assessment process

Other controls include vendor audits, qualification of vendors, etc……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Potential risk areas for emerging products

- Source Material:
  - Master cell (seed) bank – qualification, adventitious agent concerns, criticality of propagation control
  - Transgenic or Transfected Plants - propagation control issues, level of experience with system used, adventitious agent concerns
  - Biologic sourced – ascites, plasma or tissues, adventitious agent concerns
- Overall robustness of source material for subsequent processing

Propagation: Testing

Fermentation and Cell Culture Conditions such as:

- pO_2, pCO_2, pH, temperature (cell growth and viral induction in some instances),
- agitation rate (nutrient availability and product shearing effects if extracellular), and
- culture purity (and mycoplasma for eukaryotic cell culture).

Potential risk areas for emerging products

- Crude Harvest
  - Stability of drug substance under operating conditions
- Purification
  - Numerous potential concerns due to criticality of operations. Hazards vary depending upon nature of unit operation.
- Finishing
  - Numerous potential concerns based on nature of operations, route of patient administration, and nature of clinical presentation

Purification Operations: Risk Examples

Equipment Use Conditions such as:

- Packing and bioburden of chromatographic resins (impurity profile effects and sensitizing agents or degradation effects)
- Permeate flow rates and bioburden for TFF units (separation capability and sensitizing agents/degradation effects)

Equipment Status Risks

Factors that play a role in the risk management for equipment:

- Conditions utilized in routine processing and equipment capability within that context
- Level of recoverability for potential product hazards
- Includes critical environment control capability (HVAC, pharmaceutical grade water, etc.) – dependence of process control over surrounding environment and actions performed by personnel

Risk Mitigation: In-Process Testing

Factors that play a role in the extent of in process testing includes:

- Complexity of each unit operation
- Variability of equipment function as it supports the unit operation
- Sensitivity of process stream to known factors (immunogenicity, sensitizing agents, etc.)

Risk: Equipment and Process Capability Assessment

- Has each unit operation been assessed for suitability of equipment and process stream contacts? (i.e., under operating conditions)
- Has each unit operation that is critical for safety of the product been validated? (e.g., sterilization of final container closure system components)

Risk: Equipment and Process Capability Assessment

- Performance testing in place where needed? (performance capability demonstrated via appropriate qualification, validation, and/or routine manufacturing data)

Risk & Equipment Capability Assessment

- Filtration/Concentration steps controlled ?
- Routine use of purification columns controlled ?
- Any rework or reprocessing steps in the process due to potential equipment function concerns ? If so, are they validated ? (speaks to “recoverability of process” due to potential hazards)

Why minimize bioburden additions to the process stream ?

- Risks associated with microbial metabolites or cellular components that may either degrade product or introduce sensitizing agents to the final drug product

Risk Mitigation: Bioburden Control - 1

- Achieved via minimizing bioburden additions to the process stream through equipment and procedural controls over the manufacturing process

Risk Mitigation: Bioburden Control - 2

- Bioburden control of each manufacturing unit operation should be carefully considered throughout process development
- This will often include a combination of sterilization and sanitization of equipment and other process stream contact materials

Risk Mitigation: Environmental Monitoring

- Are the controlled production environments appropriate to support the manufacturing processes being performed? Especially for open product manipulations and aseptic operations.
- Critical utilities appropriately maintained and qualified / requalified ?
- Preventative maintenance and calibration programs appropriate ?


A QUALITY PRODUCT
QA/QC –Verification of successful *Risk Mitigation*
Validation / Qualification
Routine Monitoring
Risk Assessment
Equipment
Environment
Process
Raw Materials
Components

Risk Mitigation: Purpose of Testing

To verify that all processes and systems continue to function (as designed) on a routine basis …

AND

…that product meets quality expectations reflecting clinical experience.

Risk Mitigation: Testing Program

The process is dynamic and varies from product to product. For example:

- Suitability of raw materials
- Operating status of equipment/facility/personnel supporting a unit operation
- Suitability of material generated by a unit operation for continued production
- Suitability of final product for use

Testing: Formulation / Finishing Operations

- Weight checks on excipients and active(s), verification of equipment status through tags, etc.
- Fill equipment checks (usually combination of parametric and procedural verification, such as monitoring temp and blow rates of dry heat tunnels and verification of sanitization of critical zones, bubble points on sterile filters, etc.)
- Fill volume/weight checks
- Aseptic filling operations utilized for almost all biotechnology-derived products


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Process Validation

- Do the unit operations include operating parameters based upon the validation studies?
- Are fitness-for-use criteria well defined for all materials involved in processing?
- Do the process validation studies address high priority risk factors and hazards?

Validation – What if studies fail?

- Sterility assurance validation studies and aseptic processing qualification studies (e.g., media challenges) completed ?
- Are cleaning validation studies appropriate for the context of use for the equipment ? Does validation approach include potential for highly biologically active cross contamination or adventitious agents (as appropriate) ?
- Are computer and PLC controlled systems appropriately controlled (and validated, if necessary) ?
- Are “closed” systems appropriately qualified ?

Components and other Risks

- Diluent formulation: Any hazards related to reconstitution, clinical use, end product stability ?
- Clinical administration kit components that require qualification ?
- Container closure system qualified ?
- Vendors for any components evaluated and qualified? What if they fail to perform?
- Documentation for release appropriate ? What if quality unit fails?

Other Risks to Consider: Not always apparent during process mapping…

- Legacy Systems
- Quality Oversight problems
- Variability: Personnel performance/training, equipment and utilities, raw materials, contract partners and vendors, etc.

Risk Assessment: Legacy Systems and New Technologies

- If “legacy” equipment or facility being utilized, is the approach rigorous based upon known prior uses, or lack of prior use information? Risk assessment difficult when previous use history of equipment is unknown
- When implementing new technology, has it been thoroughly consider in the context of use?
- Have the considerations taken into account during protocol design been *documented* ?

Risk concerns are not always apparent during process mapping

- Contract Manufacturing: Operations outside your direct control
- **Risk Mitigation? -** ***Very careful choice of contract partners*** and vendors including "track history

Risk Mitigation: Contract Partners and Quality Agreements

- Do the quality agreements between the applicant and any contract manufacturer include adequate reporting of deviations not directly related to product manufacture?

Risk Mitigation: Contract Partners and Quality Agreements

- Does change control system of the contract manufacturer include notification of applicant and/or direct involvement of applicant in implementation decision?
- Example: Does introduction of an investigational product operation into areas utilized for contract manufacturing include applicant notification?

Important Aspect of Risk Mitigation: Contract Partners and Quality Agreements

- Experienced and knowledgeable staff – manufacturing AND quality units

Process Mapping

Risk Assessment

Possible Control Parameters

Risk Mitigation

Development Studies / Initial Validation Studies

***Initial* Critical Control Parameters**

Conformance Study / Lifecycle Revalidation

Process Control

Risk Management

Risk Based Product Quality!

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Summary - 1

- Risk assessment is a means to identify potential hazards to the process and product, both prospectively and in a reactive mode.
- There are a variety of informal and formal means to perform risk management related activities.

Summary - 2

- A thorough process mapping exercise followed by thorough risk management may lead to:
  - A more rationale and comprehensive master validation plan through enhanced process understanding;
  - A more efficient developmental plan for the commercial process;
  - Less duplication of effort in validation and qualification activities, especially when implementing emerging technologies;

Summary - 3

- A thorough process mapping exercise followed by thorough risk management may lead to:
  - Increased robustness in process capability when rationale risk mitigation is being practiced; and
  - Completion of a more rigorous and well rounded series of process validation studies.

Sources of Information

- Various documents including:
  - FDA public presentations on the GMP initiative, risk assessment and quality system approaches
  - Working draft versions of ICH Q8 and ICH Q9
  - CBER experience in pre-approval and pre-license inspection findings
  - CBER experience in product development discussions
  - Compliance Policy Guide 7132c.08

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